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Randomized Clinical Trial

Preoperative high dose of dexamethasone in emergency laparotomy: randomized clinical trial

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Abstract

Background: Patients undergoing emergency laparotomy present with a profound inflammatory response, which could be an independent pathophysiological component in prolonged recovery. The aim of this study was to investigate the effects of a single preoperative high dose of intravenous dexamethasone on the inflammatory response and recovery after emergency laparotomy.

Methods: In this double-blinded placebo-controlled trial, patients were prospectively stratified according to surgical pathology (intestinal obstruction and perforated viscus) and randomized to preoperative 1 mg/kg dexamethasone or placebo at a ratio of 1 : 1. The primary outcome was C-reactive protein on postoperative day 1. Secondary outcomes were postoperative recovery, morbidity, and mortality.

Results: A total of 120 patients were included in the trial. On postoperative day 1, the C-reactive protein response was significantly lower in the dexamethasone group (a median of 170 *versus* 220 mg/l for dexamethasone and for placebo respectively; $P = 0.015$; mean difference = 49 (95% c.i. 13 to 85) mg/l) and when stratified according to intestinal obstruction (a median of 60 *versus* 160 mg/l for dexamethasone and for placebo respectively; $P = 0.002$) and perforated viscus (a median of 230 *versus* 285 mg/l for dexamethasone and for placebo respectively; $P = 0.035$). Dexamethasone administration was associated with improved recovery (better haemodynamics, better pulmonary function, less fatigue, and earlier mobilization). Furthermore, the dexamethasone group had a lower 90-day mortality rate (7% *versus* 23% for dexamethasone and for placebo respectively; relative risk 0.33 (95% c.i. 0.11 to 0.93); $P = 0.023$) and a decreased incidence of postoperative major complications (27% *versus* 45% for dexamethasone and for placebo respectively; relative risk 0.62 (95% c.i. 0.37 to 1.00); $P = 0.032$).

Conclusion: A single preoperative high dose of intravenous dexamethasone significantly reduces the inflammatory response after emergency laparotomy and is associated with enhanced recovery and improved outcome.

Registration number: NCT04791566 (http://www.clinicaltrials.gov).

Key points

Question: Can a single preoperative high dose of dexamethasone attenuate the inflammatory response after emergency laparotomy for intestinal obstruction and perforated viscus?
Findings: In this RCT of 120 patients undergoing emergency laparotomy, preoperative 1 mg/kg dexamethasone significantly reduces inflammation and is associated with improved recovery and postoperative morbidity and mortality.
Meaning: First evidence of potential therapeutic benefit of high-dose intravenous dexamethasone in emergency laparotomy.

Introduction

The burden of non-trauma emergency general surgery is significant, accounting for approximately 10% of total surgical cases, but 50% of all surgical deaths[1]. Emergency laparotomy, defined as the surgical exploration of the abdomen by either laparotomy or laparoscopy for a number of underlying acute pathologies, such as intestinal obstruction and perforated viscus, is a significant contributor to this burden[2].

Patients undergoing emergency laparotomy often have limited physiological reserves[3,4] and a high incidence of frailty[5], resulting in an increased risk of postoperative complications and death[6]. Research in optimizing perioperative care in emergency laparotomy has primarily focused on perioperative logistics and providing standardized care[3,7], but little attention has been paid with regard to modifying the perioperative inflammatory response to facilitate early recovery[4].

The impact of surgical trauma on the immune system is multifactorial, affecting cellular functional changes at different levels in both the innate and adaptive arms of the immune system[8]. The accompanying inflammation results in increased capillary permeability, leading to tissue oedema, postoperative overhydration, and subsequent organ dysfunction, as seen frequently in emergency laparotomy[9]. Most analyses to date use

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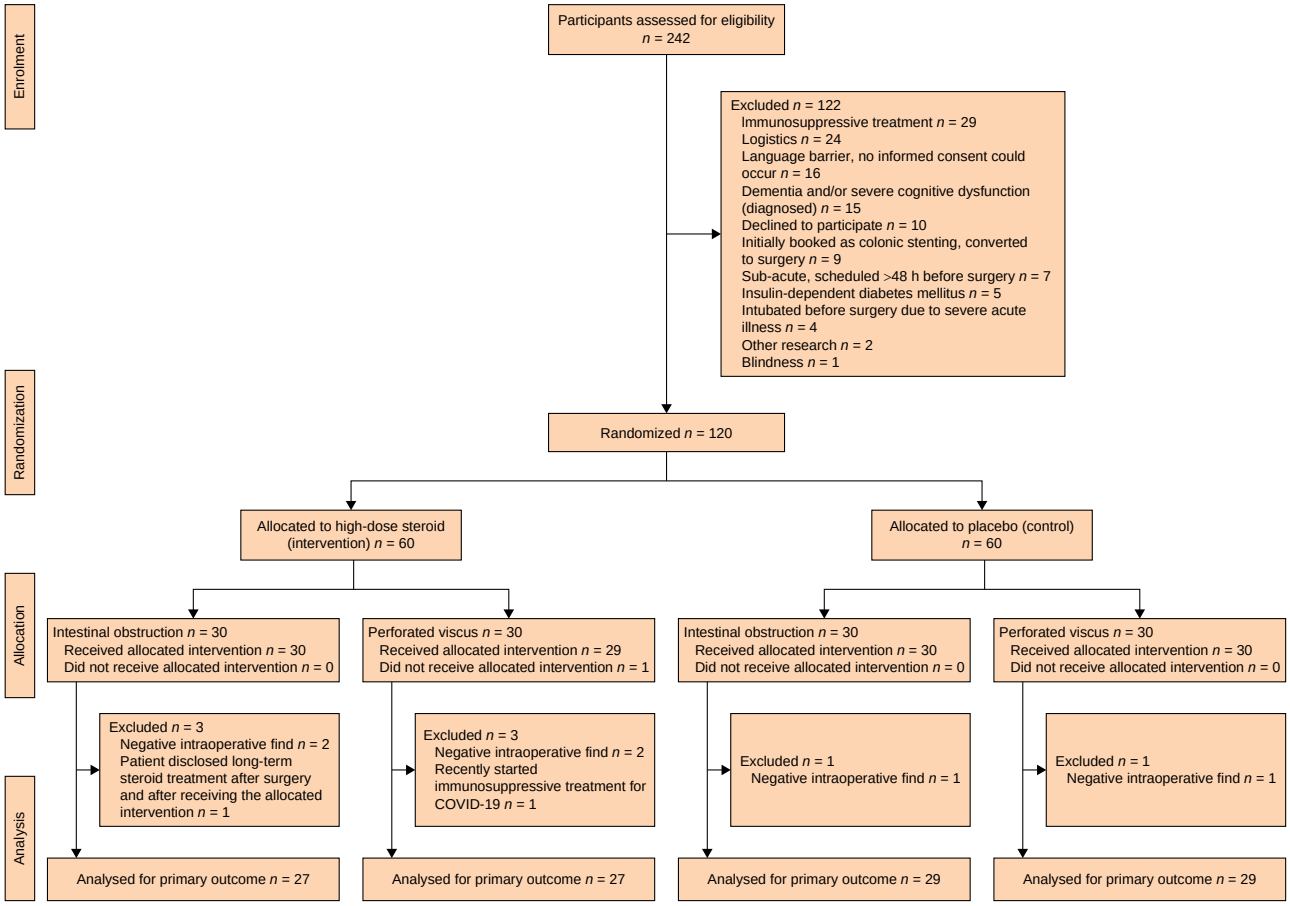
Enrolment
Participants assessed for eligibility n = 242
Excluded n = 122
Immunosuppressive treatment n = 29
Logistics n = 24
Language barrier, no informed consent could occur n = 16
Dementia and/or severe cognitive dysfunction (diagnosed) n = 15
Declined to participate n = 10
Initially booked as colonic stenting, converted to surgery n = 9
Sub-acute, scheduled >48 h before surgery n = 7
Insulin-dependent diabetes mellitus n = 5
Intubated before surgery due to severe acute illness n = 4
Other research n = 2
Blindness n = 1
Randomization
Randomized n = 120
Allocated to high-dose steroid (intervention) n = 60
Allocated to placebo (control) n = 60
Allocation
Intestinal obstruction n = 30
Received allocated intervention n = 30
Did not receive allocated intervention n = 0
Perforated viscus n = 30
Received allocated intervention n = 29
Did not receive allocated intervention n = 1
Intestinal obstruction n = 30
Received allocated intervention n = 30
Did not receive allocated intervention n = 0
Perforated viscus n = 30
Received allocated intervention n = 30
Did not receive allocated intervention n = 0
Analysis
Excluded n = 3
Negative intraoperative find n = 2
Patient disclosed long-term steroid treatment after surgery and after receiving the allocated intervention n = 1
Excluded n = 3
Negative intraoperative find n = 2
Recently started immunosuppressive treatment for COVID-19 n = 1
Excluded n = 1
Negative intraoperative find n = 1
Excluded n = 1
Negative intraoperative find n = 1
Analysed for primary outcome n = 27
Analysed for primary outcome n = 27
Analysed for primary outcome n = 29
Analysed for primary outcome n = 29

Fig. 1 CONSORT flow chart

plasma C-reactive protein (CRP)[10,11] to assess the impact of different levels of inflammation on short-term surgical and infectious complications[12–14] and longer-term overall survival[15,16].

Administration of glucocorticoids in the perioperative setting has primarily been used to reduce postoperative nausea and vomiting. Recently, studies in elective surgery have indicated that higher doses of corticosteroids have the potential to reduce excessive systemic inflammation, with a reduction in postoperative pain and early fatigue, without signals indicating harm[17–19]. The potential benefits of glucocorticoids have yet to be explored in emergency laparotomy.

The physiological effects of perioperative corticosteroids are procedure-, timing-, and dose-specific[8]. The aim of this trial was to evaluate the potential of a single preoperative high dose of glucocorticoids for attenuating inflammatory response and subsequent effects on recovery and morbidity after emergency laparotomy for intestinal obstruction and perforated viscus.

Methods

Trial design and participants

This single-centre randomized double-blinded placebo-controlled intervention was conducted at Hvidovre University Hospital, Denmark, from 3 March 2021 to 25 September 2022. The trial protocol, designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[20] and published accordingly[21], is available as *Supplementary material*. The protocol was registered at clinicaltrials.gov (NCT04791566), approved by the Danish Regional Committee on Research Ethics (H-20038432), the Danish Data Protection Agency (P-2020-715), the Danish Medicines Agency (2020-062981), and the European Medicines Agency (2020-002586-34), and conducted following the Helsinki Declaration and monitored by The Good Clinical Practice Unit at Copenhagen University Hospital. CONSORT recommendations[22] were followed; see *Fig. 1* for the CONSORT flow chart.

Adult patients scheduled for emergency laparotomy for either intestinal obstruction or perforated viscus were eligible. Exclusion criteria were reoperations after elective or emergency surgery, traumas, gynaecological, urogenital, and other vascular pathology, dementia and/or diagnosed cognitive dysfunction, insulin treatment for diabetes, immunosuppressive treatment, current treatment of cancer, allergy toward the study medication, pregnancy, and lack of informed consent.

Recruitment

After a confirmed CT diagnosis of either intestinal obstruction or perforated viscus, the senior surgeon contacted the primary investigator (PI). The PI evaluated and informed the patients, securing written and verbal consent before surgery and before arrival at the operating room. The PI of the trial evaluated and included all patients (*Fig. S1a*).

Randomization and masking

Sequence generation and preparation of 120 sequentially numbered opaque sealed randomization envelopes were completed by two

people independent of the research team and who had no further role in the trial. The participants were stratified according to surgical diagnosis (intestinal obstruction or perforated viscus) and then randomly assigned at a ratio of 1 : 1 to the intervention group or the placebo group. Personnel, not otherwise involved in the trial and with no prior knowledge regarding the creation of the envelopes or the randomization sequence, opened the randomization envelopes, prepared and blinded the trial medication, and sealed the envelopes again afterwards (including a signature on the back of the envelope) for storage until all study analyses were completed. Patients, care providers, and data collectors were blinded to allocation. Randomized patients did not receive additional dexamethasone (DXM) as a postoperative nausea and vomiting prophylactic.

Perioperative management

Following a well-established multimodal standardized protocol[7], and adhering to current emergency laparotomy audit guidelines[23,24], invasive haemodynamic monitoring, including stroke volume-guided fluid and vasopressor management (LiDCO*rapid*™; LiDCO, London, UK), was applied to all patients during the intraoperative interval and during post-anaesthesia care unit (PACU) or ICU stay. Patients received epidural analgesia when not contraindicated and total intravenous anaesthesia with propofol and remifentanil.

All patients were allocated to the PACU for intermediate care for up to 24 h after surgery, unless directly admitted to the ICU. Further postoperative treatment in the surgical ward included optimal pain treatment, early nutrition, and mobilization[7].

Intervention

Enrolled patients received one of two treatments, a single preoperative dose of 1 mg/kg DXM or placebo, diluted in 100 ml of physiological saline and administered just after anaesthesia induction as a 15-min infusion.

Patients' physiological data and CRP values were assessed during the preoperative optimization, 6 h after surgery, and on postoperative day (POD) 1, POD 3, and POD 5. Clinical outcomes were: fluid balance, defined as the difference between total input and total output (not including insensible losses); total body water and extracellular water volumes, estimated using bioimpedance spectroscopy[25], and differentiating between dehydration, normal hydration, and over hydration by calculating relative fluid overload; haemodynamics, namely the measurement of dynamic parameters (stroke volume, cardiac output, and systemic vascular resistance) and static parameters (mean arterial pressure and heart rate), with continuous invasive and non-invasive haemodynamic monitoring of arterial pressure[26]; and pulmonary function, namely the measurement of peak expiratory flow, defined as the maximal flow rate achieved during forceful expiration after full inspiration (sitting and standing)[27] (*Fig. S1b*).

Postoperative fatigue was assessed using the numeric five-point verbal rating scale (0, no fatigue; 1, mild; 2 moderate; 3 severe; and 4, bedbound by fatigue), mobilization was assessed using the cumulated ambulatory score[28] (0–6 scale, measuring the level of independence in getting in and out of bed, going from sitting in a chair to standing, and walking with or without an appropriate walking aid), and pain during mobilization was assessed using the numeric rating scale (0–10 scale, with 0 meaning 'no pain' and 10 meaning 'the worst pain imaginable').

Patients were observed for serious side effects of DXM (delirium, incidence of new episode of sepsis, invasive fungal infection, clinically important gastrointestinal bleeding, postoperative surgical infection, anaphylactic reaction to intravenous glucocorticoids, hyperglycaemia, and incidence of ketoacidosis).

Outcome assessment

The primary outcome was plasma CRP on POD 1. The understanding of the relationship between excessive systemic inflammation and surgical outcomes is largely based on research into postoperative CRP concentrations[10,11,13]. In response to inflammation, infection, and injury, CRP trajectory has a steep incline in patients undergoing emergency laparotomy[29] and CRP is considered and utilized as a surrogate for inflammatory response and severe tissue damage[14,16]. Secondary outcome measures were plasma CRP during the later postoperative interval, hydration status, haemodynamics, peak expiratory flow, postoperative fatigue, mobilization, and delirium (via confusion assessment method[30]), 30-day postoperative morbidity, 30- and 90-day mortality, ICU admission, and duration of hospital stay.

Major postoperative complications were registered according to Clavien–Dindo classification[31], specifically: pulmonary (pulmonary oedema, ultrasound-guided pleural drainage, ICU admission due to respiratory failure), gastrointestinal (emergency reoperations for intestinal obstruction, perforated viscus, anastomotic leakage, or surgical wound infection, emergency endoscopy for bleeding ulcer, and ultrasound-guided drainage of intra-abdominal abscess), and renal (acute kidney injury, need for renal replacement therapy, and Rifle criteria for acute kidney disease)[32].

Statistics

Studies assessing the effects of glucocorticoids have shown a postoperative reduction in CRP of between 50% and 85%[17,33]; however, these studies did not involve emergency laparotomy. Calculation of power and sample size for this trial was based on CRP values from a recent cohort study of patients undergoing emergency laparotomy[29] done at the trial site centre. The hypothesis of this study was that DXM would lead to a reduction in the postoperative mean CRP value of 50%. To detect a type I error rate of 5% (two-tailed) with a statistical power level of 80%, a sample size of 40 patients in each group was required. The sample size was increased to 120 to allow for dropouts.

Not all patients were assessable for the primary outcome, demanding a per-protocol analysis. Therapeutic gain was estimated using the chi-squared test, including calculation of relative risks (RRs), with 95% confidence intervals. Assessment of dropouts was performed before the randomization code was broken. Comparisons between the two groups were performed using the Mann–Whitney *U* test for continuous data and the chi-squared test or Fisher's exact test for dichotomous categorical variables. $P < 0.050$ was considered statistically significant. The unadjusted and adjusted ORs were calculated as part of regression analysis of morbidity and mortality. Secondary outcomes were treated as exploratory. All analyses were performed using R statistical software. (www.rproject.org).

Results

Study participants

A total of 400 patients were assessed for eligibility; 120 fulfilled the inclusion criteria and were randomized (60 with intestinal obstruction and 60 with perforated viscus). A total of eight patients were subsequently excluded (six due to negative intraoperative pathology, one due to after-inclusion discovery of having recently started immunosuppressive treatment for COVID-19, and one due to disclosing long-term steroid treatment after receiving the

Table 1 Baseline characteristics and procedural data

Variables	Dexamethasone ($n = 54$)	Placebo ($n = 58$)
Characteristics		
Age (years), median (i.q.r.)	71 (57–78)	68 (54–76)
Female	30 (55.5)	32 (55.2)
BMI (kg/m^2), median (i.q.r.)	26 (23–30)	26 (22–29)
ASA grade >II	24 (44.4)	26 (44.8)
ECOG performance status >1	13 (24.1)	17 (29.3)
Charlson co-morbidity index ≥3	24 (44.4)	22 (38.0)
qSOFA score >1	8 (14.8)	13 (22.4)
Co-morbidities		
Cardiovascular (IHD or HF)	5 (9.3)	9 (15.5)
Chronic hypertension	18 (33.3)	17 (29.3)
Pulmonary	12 (22.2)	9 (15.5)
Cerebrovascular	6 (11.1)	2 (3.4)
Renal	3 (5.5)	3 (5.2)
Malignancy	2 (3.7)	3 (5.2)
Preoperative laboratory values		
Sodium (mmol/l), mean(s.d.)	137(4)	137(4)
Potassium (mmol/l), mean(s.d.)	3.8(0.4)	3.8(0.4)
Chloride (mmol/l), median (i.q.r.)	106 (101–107)	104 (101–107)
Albumin (g/l), median (i.q.r.)	33 (27–36)	31 (27–37)
White blood cells (10^9/l), mean(s.d.)	11.6(4.3)	12.0(5.3)
C-reactive protein (g/l), median (i.q.r.)	40 (5–190)	51 (9–130)
Creatinine (mmol/l), median (i.q.r.)	75 (63–95)	78 (64–93)
Lactate (mmol/l), median (i.q.r.)	0.8 (0.6–1.2)	1.0 (0.1–1.8)
pH, mean(s.d.)	7.42(0.1)	7.42(0.1)
Bicarbonate (mmol/l), mean(s.d.)	24.7(2.8)	24.8(6.8)
Intraoperative data		
Intestinal obstruction	27 (50.0)	29 (50.0)
Perforated viscus	27 (50.0)	29 (50.0)
Epidural analgesia	48 (88.8)	45 (77.6)
Laparoscopy	24 (44.4)	21 (36.2)
Laparotomy	30 (55.5)	37 (63.8)
Duration of surgery (min), median (i.q.r.)	83 (65–151)	102 (66–159)
Manheim peritonitis index, median (i.q.r.)	16 (10–21)	16 (11–23)
Malignancy discovered during surgery	5 (9.3)	10 (17.2)

Values are *n* (%) unless otherwise indicated. i.q.r., interquartile range; ECOG, Eastern Cooperative Oncology Group; qSOFA, quick sequential organ failure assessment; IHD, Ischemic Heart Disease; HF, Heart Failure.

intervention) (*Fig. 1*). The eight dropouts were part of the intention-to-treat analysis. The inclusion rate was 50%. Patient characteristics and procedural data were similar between the groups (*Table 1*) and when stratified according to surgical diagnosis (*Tables S1, S2*). There were no missing data.

Primary outcome

Overall, 112 patients were evaluated for the primary outcome. DXM led to a reduction in absolute values of CRP on POD 1, with a median of 170 (interquartile range (i.q.r.) 60–260) mg/l, compared with a median of 220 (i.q.r. 150–300) mg/l for placebo ($P = 0.015$) (*Fig. 2*). DXM led to a reduction in CRP in both intestinal obstruction (a median of 60 (i.q.r. 30–160) mg/l for DXM *versus* a median of 160 (i.q.r. 100–220) mg/l for placebo; $P = 0.002$) and perforated viscus (a median of 230 (i.q.r. 170–280) mg/l for DXM *versus* a median of 285 (i.q.r. 200–330) mg/l for placebo; $P = 0.035$) (*Fig. 2*).

Secondary outcomes

Patients allocated to placebo showed a consistently higher positive fluid balance, compared with patients allocated to DXM (*Fig. 3a*), with a median of 6.2 (1.7–8.4) *versus* 3.5 (1.0–7.4) l respectively ($P = 0.015$) on POD 5. The same trend was observed when patients were stratified according to surgical diagnosis (*Fig. S3*). Patients allocated to DXM were less overhydrated than patients allocated to placebo; the incidence of overhydration was 44.1% *versus* 63.3% respectively ($P = 0.034$) on POD 5 (*Fig. 3b*). Again, the same trend was observed when patients were stratified according to surgical diagnosis, although with a more pronounced difference in patients with intestinal obstruction (*Fig. S4*).

Patients allocated to DXM had reduced pain scores during mobilization, reduced postoperative fatigue, a higher level of independence in getting in and out of bed, and better lung function, compared with patients allocated to placebo (*Fig. 3c–f*). When patients were stratified according to surgical diagnosis (*Fig. S5*), the trend was the same, albeit more pronounced in patients with intestinal obstruction.

Finally, better haemodynamic status was observed in patients allocated to DXM (*Fig. S6*), compared with patients allocated to placebo, with a lower incidence of vasopressor need during the postoperative interval (3 (5.5%) *versus* 11 (19.0%) patients with vasopressor need beyond 24 h after surgery; $P = 0.021$; RR 0.27 (95% c.i. 0.08 to 0.92)) (*Table 2*).

The observed 30-day mortality rate was 7.4% in the DXM group and 12.1% in the placebo group ($P = 0.410$; RR 0.61 (95% c.i. 0.19 to 1.98)) (*Table 2*). The observed 90-day mortality was 7.4% in the DXM group and 22.4% in the placebo group ($P = 0.023$; RR 0.33 (95% c.i. 0.11 to 0.95)). The unadjusted OR for 90-day mortality associated with DXM was 0.27 (95% c.i. 0.10 to 0.84). When adjusted for age, ASA grade, performance status, sepsis, surgical technique, and duration of surgery, the OR was 0.22 (95% c.i. 0.10 to 0.87) (*Table S3*).

In total, 15 (27.7%) and 26 (44.8%) patients had at least one major postoperative complication in the DXM group and the placebo group respectively ($P = 0.032$; RR 0.62 (95% c.i. 0.37 to 1.00)) (*Table 2*). The unadjusted OR for major complications associated with DXM was 0.47 (95% c.i. 0.21 to 1.00). When adjusted for age, ASA grade, performance status, sepsis, surgical technique, and duration of surgery, the OR was 0.44 (95% c.i. 0.20 to 1.00) (*Table S3*).

In total, 23 serious adverse events were registered (*Table S4*), none related to the study drug. There was no difference in the incidence of delirium (14.8% in the DXM group *versus* 10.3% in the placebo group; $P = 0.475$; RR 1.40 (95% c.i. 0.53 to 3.86)), new onset of sepsis (3.7% in the DXM group *versus* 5.2% in the placebo group; $P = 1.000$), or reoperation for surgical wound infection (7% in the DXM group *versus* 9% in the placebo group; $P = 1.000$; RR 0.84 (95% c.i. 0.24 to 2.98)). Compared with the placebo group, the median blood glucose levels were higher in the DXM group 6 h after surgery ($P = 0.001$) and remained higher on POD 1 ($P < 0.001$) and POD 2 ($P = 0.025$), with a downward trajectory (*Fig. S7*). No instances of diabetic ketoacidosis were reported.

The intention-to-treat analysis of 120 patients (60 in the DXM group and 60 in the placebo group) regarding 30- and 90-day mortality, postoperative complications, and ICU admission did not change the results (*Table S5*).

Discussion

In this RCT of patients undergoing emergency laparotomy, the administration of a single preoperative high dose of DXM significantly reduced CRP 24 h after surgery, with the effect lasting into POD 3. This reduction was associated with several positive effects on the secondary outcomes of postoperative recovery.

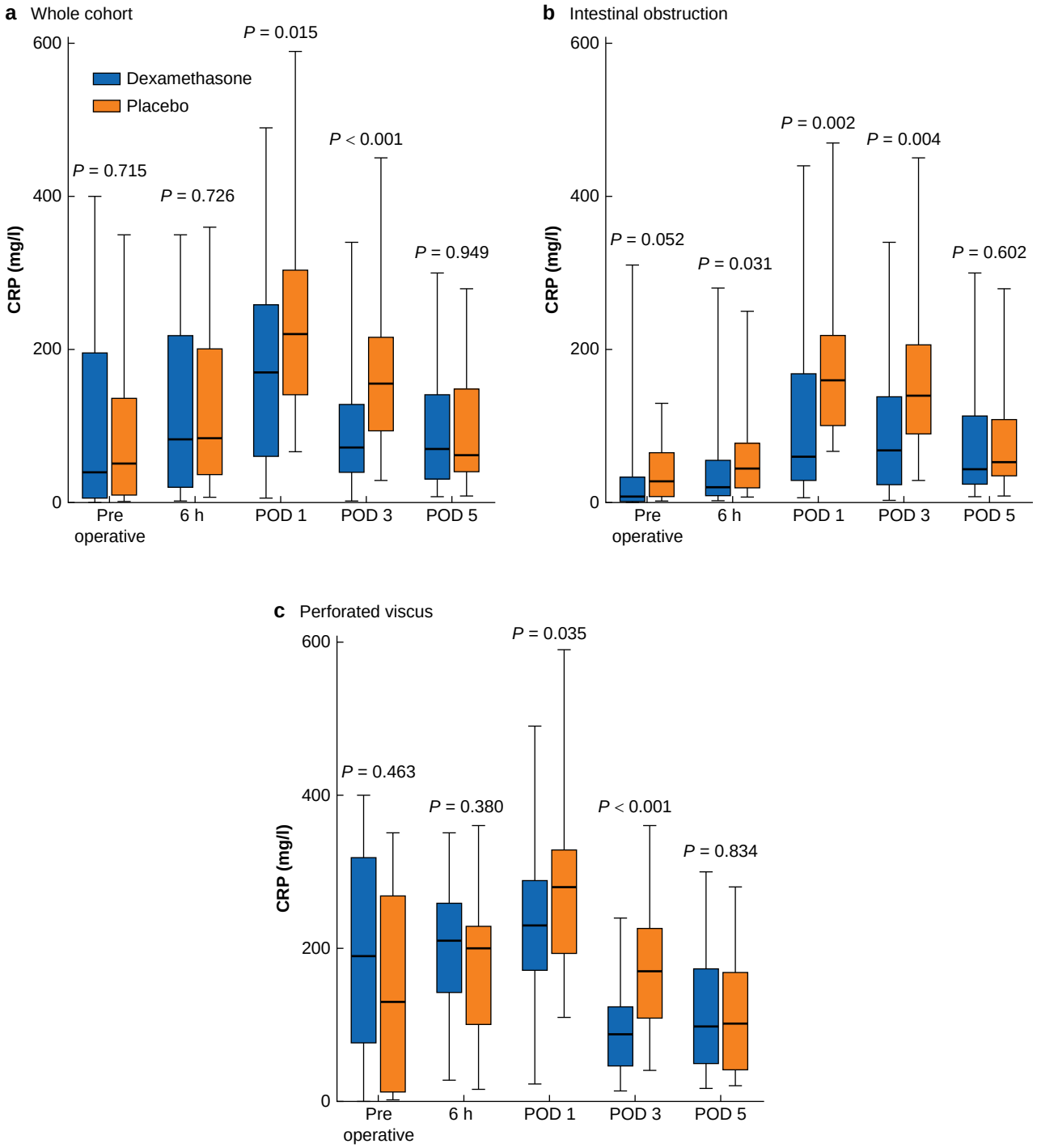

Fig. 2 C-reactive protein levels during the perioperative interval (absolute values)

The boxes represent the interquartile ranges, the horizontal lines represent the median values, and the whiskers represent the minimum and maximum values. The Mann–Whitney *U* test was applied. CRP, C-reactive protein; POD, postoperative day.

In addition to improved haemodynamics and a lower incidence of overhydration, the reduced inflammatory response in the DXM group was associated with lower cumulative postoperative fatigue and pain scores, and more independent mobilization, compared with the placebo group. Importantly, while this trial was not powered to demonstrate a potential benefit of DXM regarding morbidity and mortality, there was an apparent association supported by the regression analysis, with no indication of harm.

The implementation of care bundles has been instrumental in reducing mortality in emergency laparotomy[7,34]. Still, studies report an incidence of postoperative major complications greater than 40% and little impact on duration of hospital stay[4,35,36], with no specific data regarding perioperative interventions that could improve recovery as has been shown in elective surgery[37].

The systemic inflammatory response after major surgery is strongly indicative of the progression to hyperinflammation or dysregulation during the postoperative interval[18] and is associated with wound infections, as well as pulmonary and cardiac complications. The best evidence on the effectiveness of higher doses of corticosteroids on outcome originates from two large

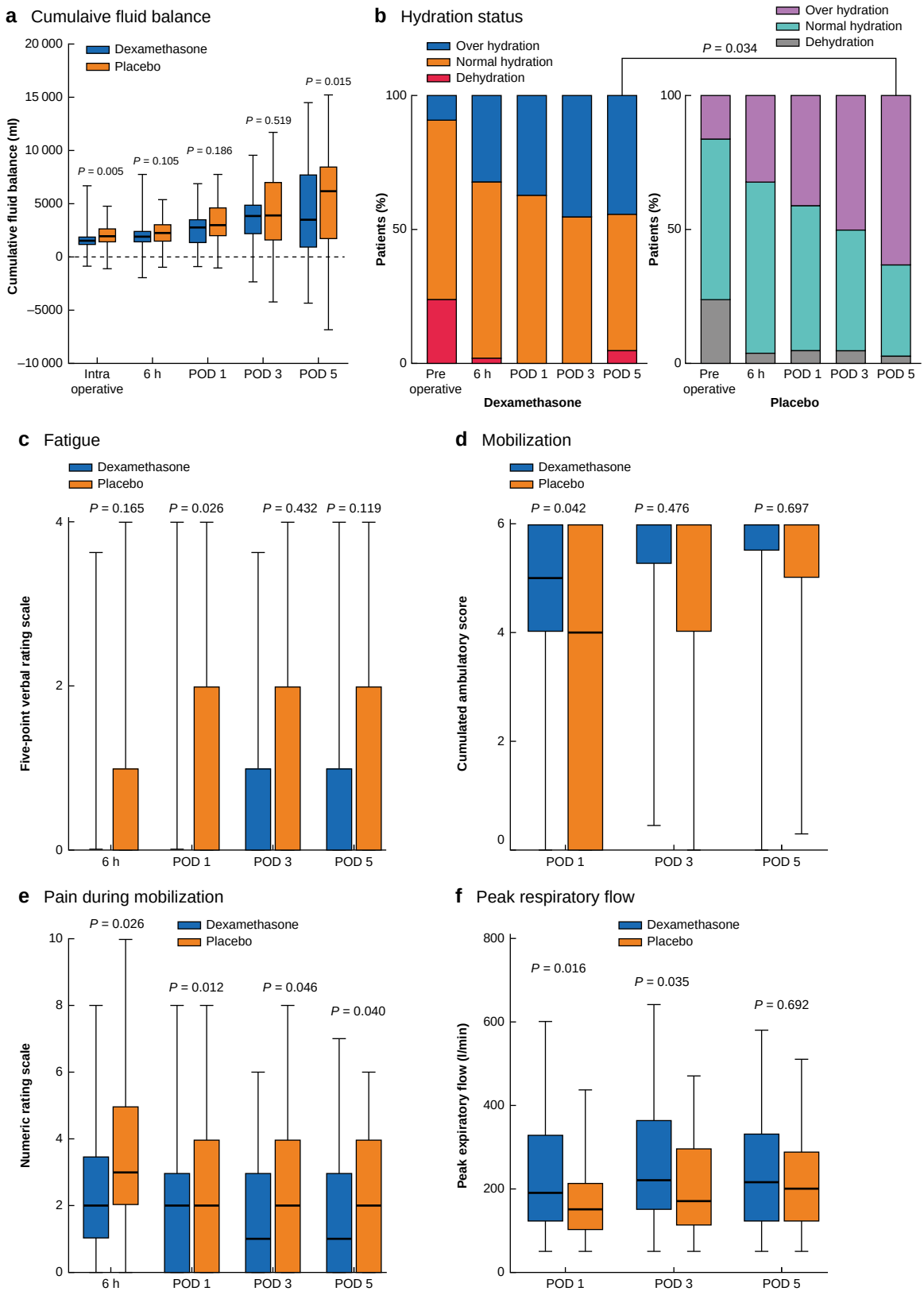

Fig. 3 Recovery: cumulative fluid balance, hydration status, fatigue, mobilization, and pain scores, and peak expiratory flow

a Cumulative fluid balance during the perioperative interval. **b** Hydration status (measured using bioimpedance spectroscopy) during the perioperative interval (dehydration (relative fluid overload less than -10%), normal hydration (relative fluid overload greater than or equal to –10% and less than or equal to +15%), and overhydration (relative fluid overload greater than 15%)). **c** Fatigue (measured using the five-point verbal rating scale (0, no fatigue; 1, mild; 2, moderate; 3, severe; and 4, bedbound by fatigue)). **d** Mobilization (measured using the cumulated ambulatory score (0–6 scale, measuring the level of independence in getting in and out of bed, going from sitting in a chair to standing, and walking with or without an appropriate walking aid)). **e** Pain (measured using the numeric rating scale (0–10 scale, with 0 meaning 'no pain' and 10 meaning 'the worst pain imaginable'). **f** Peak expiratory flow. The boxes represent the interquartile ranges, the horizontal lines represent the median values, and the whiskers represent the minimum and maximum values. Mann–Whitney *U* test for statistical significance. POD, postoperative day.

Table 2 Major postoperative complications and deaths after emergency laparotomy

Variables	Dexamethasone ($n = 54$)	Placebo ($n = 58$)	P (chi-squared)	Relative risk associated with dexamethasone (95% c.i.)
Duration of hospital stay, median (i.q.r.)	8 (5–14)	9 (6–21)	0.380*	–
Thirty-day mortality	4 (7.4)	7 (12.1)	0.410	0.61 (0.19,1.98)
Ninety-day mortality	4 (7.4)	13 (22.4)	0.023	0.33 (0.11,0.95)
Patients with at least one 30-day major complication (CD >II)	15 (27.7)	26 (44.8)	0.032	0.62 (0.37,1.00)
Overall surgical-site infections, minor and major	7 (12.9)	8 (13.8)	0.990	0.90 (0.25,2.99)
Overall non-surgical infections, minor and major	19 (35.2)	26 (44.8)	0.185	0.66 (0.34,1.35)
Vasopressor need 6 h after surgery	11 (20.4)	19 (32.8)	0.173	0.65 (0.34,1.23)
Vasopressor need 24 h after surgery	9 (16.6)	19 (32.8)	0.040	0.51 (0.25,1.00)
Vasopressor need beyond 24 h after surgery	3 (5.5)	11 (19.0)	0.021	0.27 (0.08,0.92)
Ultrasound-guided pleural drainage	3 (5.5)	12 (20.1)	0.019	0.27 (0.08,0.90)
ICU admission† due to respiratory failure and need for invasive/ non-invasive ventilation	2 (3.7)	7 (12.1)	0.092	0.27 (0.06,1.21)
Reoperation for acute abdominal pathology	5 (9.3)	12 (20.1)	0.092	0.45 (0.17,1.19)
Reoperation for surgical wound infection	4 (7.4)	5 (8.6)	1.000	0.84 (0.24,2.98)
Ultrasound-guided drainage of intra-abdominal abscess	7 (12.9)	14 (24.1)	0.130	0.54 (0.23,1.23)
ICU admission† due to postoperative septic shock	3 (6)	12 (21)	0.019	0.27 (0.08,0.90)
Need for postoperative RRT	1 (2)	4 (7)	0.404	0.27 (0.03,2.33)
Incidence of delirium	8 (14)	6 (11)	0.475	1.40 (0.53,3.86)

Values are *n* (%) unless otherwise indicated. *Mann–Whitney *U* test. †Admission at any time during the first 30 days after surgery. i.q.r., interquartile range; CD, Clavien–Dindo classification of postoperative complications; RRT, renal replacement therapy.

trials in cardiac surgery and one in major non-cardiac surgery[38–40]. While none demonstrated a statistically significant benefit of corticosteroids, there was a trend toward reduced morbidity and mortality, without evidence of harm.

The physiological mechanisms of the analgesic effects and the impact on fatigue of preoperative corticosteroids can in part be explained by the reduction in inflammation[8,41], as demonstrated in this trial, where the patients showed less fatigue, reported less pain, had better pulmonary function, and were more independently mobilized in the crucial first days after surgery. These effects potentially facilitated the observed 40% relative reduction in major postoperative complications and death.

Surgical trauma induces systemic and local inflammation, oxidative stress, and changes in endothelial function. Endothelial dysfunction may therefore contribute to the demonstrated fluid changes and glucocorticoids may be instrumental in modifying the pathophysiological response of the vasculature[33]. Patients allocated to DXM had a lower incidence of vasopressor need during the early postoperative interval compared with patients allocated to placebo, suggesting an improved haemodynamic stability allready manifesting during the intraoperative period. Given the improvement in sensitivity to catecholamines after corticosteroid administration[8], DXM may allow patients to regain or maintain adequate haemodynamics and organ perfusion, and may account for the difference in fluid balance and overhydration, thus facilitating recovery. A recent meta-analysis on the effect of corticosteroids in septic patients requiring vasopressor therapy had mixed results regarding outcome[42]. However, the included trials had major heterogeneity with regard to dose, timing, and type of patients, precluding final interpretation.

The choice of high-dose DXM was based on earlier research that employed higher doses without evidence of harm[38–40]. The patient group included in the present study is known to have a profound perioperative inflammatory response and the degree to which this can be mitigated with DXM has not been investigated previously. The high dosage of DXM was chosen to explore the potential for altering the inflammatory response in patients undergoing emergency laparotomy, which would not necessarily have been revealed with lower doses.

The perioperative interval in elective surgery can be considered a controlled model to examine the efficacy of corticosteroids with regard to modifying surgical inflammatory stress, postoperative systemic inflammatory dysregulation, and subsequent outcomes. Emergency laparotomy presents a distinct contrast to this, with patients presenting with various degrees of already dysregulated systemic inflammation[9,29]. As such, the response to corticosteroids can be dependent on both the timing relative to disease progression and the surgical pathology. However, CRP was significantly suppressed in both surgical groups (intestinal obstruction and perforated viscus), supporting the effect of DXM as primarily suppressing the traumatic (surgical) response.

The inflammatory trajectory in surgery is dependent on the surgical diagnosis and the effect of the intervention will most likely have a similar heterogeneity[29]. As such, DXM managed to partially suppress the persisting response, with an eventual gradual decline in inflammation in perforated viscus, but did not achieve as profound a suppression as that achieved in intestinal obstruction. Compared with the DXM group, the median duration of surgery was longer in the placebo group, primarily influenced by perforated viscus. However, when included in the regression analysis, the duration of surgery was not an independent predictor of morbidity or mortality, and did not change the results of secondary outcomes.

Patients allocated to DXM did not have an increased rate of postoperative wound and intra-abdominal infections, or new onset of sepsis, compared with patients allocated to placebo. In contrast, the RR associated with DXM and ICU admission due to septic shock was reduced and there was no increased risk of intra-abdominal abscess drainage.

This is one of the first trials to assess a single preoperative high dose of DXM in a well-defined acute surgical population and the first trial to focus on the physiological effects in different surgical pathophysiologies. Further studies are needed, both to validate these findings and to explore the potential effects of a repeat-dose regimen in patients with inadequate suppression of the primary inflammatory response[40].

This trial has several limitations. It was a single-centre trial, with a relatively small sample size, and powered for suppression of inflammation, rather than outcome. However, the characteristics of the trial population were similar to previously published international data[7], strengthening the generalizability of the findings. It is important to underline that the secondary endpoints

are exploratory, calling for additional trials with higher numbers of patients to confirm or reject any assumptions on clinical outcomes. Notwithstanding the randomized design of this trial, the baseline difference in laparotomy *versus* laparoscopy could indicate that the placebo group was at a higher risk of complications. This was considered in the regression analysis of secondary outcomes (as well as the intention-to-treat analysis) by adjusting for confounding variables, including surgical technique (laparoscopy *versus* laparotomy). The adjustment did not seem to change the favourable effect of DXM.

The primary focus of this trial was the effect of DXM on the inflammatory response after surgery. The choice of primary outcome was based on the trajectory of the perioperative interval. Emergency laparotomy patients present with acute illness before surgery (and the surgical stress response that follows), where approximately 40%[7] fulfil the sepsis criteria. Before assessing this outcome in future studies specifically powered for it, it was necessary to evaluate whether it was at all possible to suppress the inflammatory response in these patients.

The choice of envelope randomization can be seen as a potential limitation, as it can possibly allow for subversion of the randomization. However, randomization in this trial was tightly controlled by the PI, who was at the site at every inclusion. All precautionary measures were taken to secure the allocation and all methodological information required was reported, allowing for assessment of quality.

In conclusion, a single preoperative high dose of DXM was associated with a significant reduction in the inflammatory response after emergency laparotomy, with associated improved recovery and reduction in postoperative morbidity and mortality, without clinical side effects. These findings support a potential beneficial effect of early administration of high-dose DXM to attenuate hyperinflammation and call for both exploratory and confirmatory studies with well-defined surgical pathology.

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Author contributions

Mirjana Cihoric (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft), Henrik Kehlet (Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing—review & editing), Morten Laksáfoss Lauritsen (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), Jakob Højlund (Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing—review & editing), Katrine Kanstrup (Conceptualization, Project administration, Supervision, Writing—review & editing), Sofia Kärnsund (Data curation, Investigation, Resources, Software, Writing—review & editing), and Nicolai Bang Foss (Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Anonymized trial data will be available from the corresponding author on reasonable request.

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